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(54) Title: PROCESS FOR THE SYNTHESIS OF CITALOPRAM

(57) Abstract: A new process is described for the synthesis of citalopram characterized by the conversion of 1-(4'-fluorophenyl)1-3-(dimethylaminopropyl)-5-halophthalane in the corresponding Grignard reagent; this intermediate product may be converted into citalopram via intermediate formation of an aldehyde and in the subsequent transformation of the functional group via oxime or hydrazone; or else be converted into citalopram via reaction with compounds containing a cyano group bound to a leaving group. The process described makes it possible to obtain citalopram in high yields, and does not involve the use of drastic conditions of temperature.

PROCESS FOR THE SYNTHESIS OF CITALOPRAM

FIELD OF THE INVENTION

The present invention regards of the synthesis of derivatives having a 1,3-dihydroisobenzofuran (phthalanes) structure. An efficient process is described for the synthesis of 1-[3-(dimethylamino)propyl]-1-(4-fluorophenyl)-1,3-dihydro-5-isobenzofuran-carbonitrile (citalopram).

PRIOR ART

1-[3-(dimethylamino)propyl]-1-(4-fluorophenyl)-1,3-dihydro-5-isobenzofurancarbonitrile (citalopram) was described for the first time in the patent GB-A-1 526 331. This compound is a centrally acting serotonin re-uptake inhibitor with a marked antidepressant activity (*Progr. Neuro-Psychopharmacol. & Biol. Psychiatr.*, 1982, 6, 277-295). In addition to its use in antidepressive therapy, citalopram is used in the treatment of dementia and cerebrovascular disorders (EP-A-474580). Optically active enantiomers of citalopram have been described for the treatment of obesity and alcoholism.

The structure of citalopram is illustrated by (IV) in Figure 2.

The approach most widely adopted in the synthesis of citalopram is described in Figure 1, in which a phthalide (A) is condensed with a reagent carrying a fluorophenyl group and with a reagent carrying a dimethylaminopropyl group; these condensations, carried out normally with Grignard reagents are followed by the opening of the furan ring with the formation of the diol (B); from this the furan ring is restored by dehydration. The R group is a nitrile or one of its precursor groups convertible into nitrile via cyanidation. The resulting product (C) [R=CN] is citalopram.

There exist various studies that follow the above-described synthetic approach. For example, the patent GB-A-1526 331 describes a process of synthesis of citalopram in which the derivative (A), where R = Br, is converted into (B) via reaction with Grignard reagents. This is followed by dehydration with concentrated phosphoric acid, with the formation of the product (C), and the subsequent conversion of the Br group into a CN group via reflux treatment with cuprous cyanide in dimethylformamide. According to a variant of the process, initially only one of the two condensations is performed, the intermediate product thus obtained

undergoes reduction, the ring is re-closed by dehydration, the Br group is converted into a CN group, and finally the second alkylation is performed, likewise obtaining citalopram.

These reactions lead to rather low yields (of the order of 22%), and involve the use of cuprous cyanide (a toxic compound that requires considerable precautions of use) in drastic conditions of reaction. The cyanidation reaction involves waste liquors that are difficult to dispose of on account of the presence of heavy metals and the cyanides themselves. The processing procedure is moreover very burdensome in that, for unblocking the complex, alkaline cyanides are added, and this must be followed by numerous washings of the organic reaction phase to obtain a product of acceptable quality.

EP-A-171943 re-proposes the scheme described above, using as product (A) a 5-cyanophthalide, (R = CN); in this case the cuprous cyanide is used to obtain the product (A).

In another synthesis (WO-A-9819512) the substituent R in (A) is a primary amine group: the conversion of the amine into a CN group is obtained by diazotization followed by reaction with cuprous cyanide.

WO-A-98-19513 re-proposes the scheme of synthesis described above, starting from a compound (A) in which R = alkoxycarbonyl. Although in this case the conversion of an R group into a nitrile does not require the use of cyanides, it, nevertheless, involves a long series of reactions such as hydrolysis, formation of an acyl halide, conversion to an amide and dehydration, in order to transform the R group into the cyano group.

The above-mentioned reactions present the additional disadvantage of starting from phthalides that have a high market cost, a fact that has a negative effect on the general economy of these processes.

In view of the limitations presented above, none of the syntheses so far available is totally satisfactory and there is still consequently felt the need for efficient processes having a low environmental impact for the synthesis of citalopram.

SUMMARY

A new process is described for the synthesis of citalopram characterized by the conversion of 1-(4'-fluorophenyl)1-3-(dimethylaminopropyl)-5-halophthalane into

the corresponding Grignard reagent; this intermediate product may be converted into citalopram via intermediate formation of an aldehyde and by the subsequent transformation of the functional group via oxime and hydrazone; or may be converted into citalopram via reaction with compounds containing a cyano group bound to a leaving group. The process described enables citalopram to be obtained in high yields, and does not involve the use of drastic temperature conditions.

DESCRIPTION OF THE FIGURES

Figure 1: known scheme of synthesis of citalopram

Figure 2: synthesis of citalopram starting from 1-(4'-fluorophenyl)-1-(3-dimethylaminopropyl)-5-halophthalane (I)

DETAILED DESCRIPTION OF THE INVENTION

With reference to Figure 2, a first subject of the present invention is a process of synthesis of citalopram characterized by the following steps:

(i) reaction of 1-(4'-fluorophenyl)-1-(3-dimethylaminopropyl)-5-halophthalane (I) with activated magnesium, to form the Grignard reagent of formula (I A), where X is a halogen atom, preferably bromine;

(ii) reaction of the compound (I A) with a substituted formamide, to form 1-(4'-fluorophenyl)1-3-(dimethylaminopropyl)-5-phthalane-aldehyde (II);

(iii) reaction of the compound (II) with a reagent of structure NH_2-Y, where Y is chosen from among -OH, -OCH_3, -$N(CH_3)_2$, -OSO_3H, with formation of a compound of formula (III), where Y has the aforesaid meanings;

(iv) conversion of the compound (III) into citalopram (IV).

With reference to Figure 2, the various steps of the present process are illustrated in detail as follows.

Step (i)

Step (i) of the process forming the subject of the invention consists in the conversion of 1-(4'-fluorophenyl)-1-(3-dimethylaminopropyl)-5-halophthalane (I) into the Grignard reagent of formula (I A).

By the term "halophthalane" is meant a derivative of formula (I) in which the "hal" group is an atom chosen from among bromine, fluorine, chlorine, and iodine,

Step (i) involves the reaction of the compound (I) with activated magnesium.

The compound (I) is easily synthesizeable, as, for example, is described in GB-A-1 526 331.

The activated magnesium to be used in this phase of the process is obtainable with conventional techniques, for example by reaction of metallic magnesium in chips with bromoethane or 1,2-dibromoethane, in an ether solvent such as ethyl ether, tetrahydrofuran or 2-methyltetrahydrofuran, possibly in a mixture with toluene or inert solvents, at a temperature between 25°C and the reflux temperature of the mixture.

According to a preferred embodiment of the present process, to the mixture of solvent and activated magnesium thus obtained (hereinafter defined "solution *a*"), a solution of the compound (I) is slowly added in an organic solvent, for example tetrahydrofuran (hereinafter defined "solution *b*"). The temperature of the reaction mixture is kept preferably between 40°C and 65°C.

In order to obtain high yields of the desired product, the following conditions of reaction have been found to be particularly important:

- the compound (I) is used in a molar ratio with respect to magnesium of between 3:1 and 1:1, preferably 1:2;
- the concentration of compound (I) in the solution *b* is between 0.7M and 1.2M, preferably 1M;
- the volume of the solution *a* is between 40% and 60%, preferably 50%, with respect to the volume of the solution *b*.
- the time within which the solution *b* is added is higher than 5 hours, and is preferably between 6 and 8 hours.

Step (ii)

The Grignard reagent obtained (I A) is allowed to react with a substituted formamide, thus obtaining the compound (II).

Examples of substituted formamides useful for the purposes of the present process are dimethylformamide, diethylformamide, dipropylformamide, dibutylformamide, *N*-formyl-*N*-methyl-2-aminopiridine, trimethylformyl-ethylenediamine, *N*-formylpiperidine, *N*-formylmorpholine. Dimethylformamide is preferred.

The substituted formamide is used in a molar ratio of approximately 2:1 with respect to compound (I). The temperature of the reaction mixture is between -20°C and the reflux temperature, preferably between 15°C and 50°C, or more preferably between 20°C and 25°C.

The addition time is generally between 2 and 4 hours; preferably, following on the addition, the mixture is left under stirring at room temperature for a further 1-3 hours approximately.

At the end of the process, toluene, water and possibly acid, for example glacial acetic acid, are added. From the reaction mixture the aldehyde (II) is recovered via appropriate washings.

The reaction conditions described above, in particular those regarding the use of the solutions *a* and *b*, enable the formation of reaction by-products to be reduced to a minimum, in particular those obtained by attack of the Grignard reagent on the acid sites in position 3 of the phthalane: the competitiveness of these sites in regard to the organometallic reagents is known, for example from GB-A-1526331.

All the reactions comprised in steps (i) and (ii) may be conveniently carried out in the same reactor, without need for purification of the intermediate products.

As regards the aldehyde (II) obtained at the end of Step (ii), this may be purified before being subjected to the subsequent step (iii). This purification is carried out with techniques in themselves known, such as those described in *Org. Synth.* 1955, Vol. 3, 701.

The Grignard reagent (I A) as compound per se constitutes a further subject of the present invention since it is a key intermediate product of the process described herein, which enables citalopram to be obtained in high yields and in non-drastic conditions of temperature.

Step (iii)

In step (iii), the aldehyde (II) is allowed to react with the compound NH_2-Y, (hydroxylamine or hydrazine), with formation of the compound (III) (respectively oxime or hydrazone). The specific meanings of Y have been previously indicated.

Step (iii) is carried out according to methodologies in themselves known (e.g., J. March, *Advanced Organic Chemistry*, IV ed., 1992, 367). The reaction is carried out in an appropriate organic substance, such as toluene, dimethylacetamide or

dimethylformamide at a temperature between 20°C and the reflux temperature of the mixture, preferably between 20°C and 65°C. The reaction pH must be not less than 4: every pH higher than or equal to 4 is indifferently effective.

The molar ratios between the compound (II) and the compound NH_2-Y used in this reaction are between 1:1 and 3:1, preferably being approximately 2:1.

The oxime (or hydrazone) (III) may possibly be purified before being subjected to the next step of the process; for example, when the compound NH_2-Y is used where Y is -OSO_3H (sulphonic hydroxylamine), purification is obtained by extraction of the latter in an alkaline aqueous environment.

Step (iv)

Step (iv) of the process that forms the subject of the present invention consists in the conversion of the oxime (or hydrazone) of formula (III) into the corresponding cyano derivative (IV), which is citalopram.

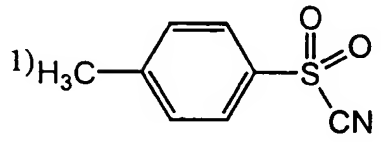
When starting from an oxime, the conversion is carried out by dehydration with a concentrated acid or with an anhydride; preferred examples are concentrated acetic acid and acetic anhydride. The dehydration is carried out at a temperature of between 50°C and the reflux temperature in an environment of organic solvent, such as toluene. The molar ratios between the compound (II) and the dehydrating compound are between 1:1 and 1:2.5.

When starting from a hydrazone, the conversion is carried out via catalysed oxidation using techniques in themselves known, as described, for instance, in *Chem. Commun.*, 19, 2145-6, 1998, or *Synthetic Commun.*, 28, 24, 4577-80, 1998. Examples of reagents used in the oxidation of hydrazones are methylrhenium trioxide and hydrogen peroxide.

Citalopram is obtained in the form of oil, from which the pure product is easily crystallized, for example via dissolution in isopropanol and crystallization from the latter. The ease of crystallization of citalopram obtained in accordance with the present process constitutes a further advantageous element of the invention in question.

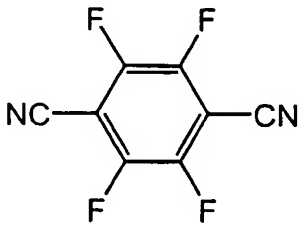
An interesting variant of the synthesis illustrated above, [see Figure 2, Steps (i)-(ii')], enables the citalopram (IV) to be obtained directly from the intermediate Grignard product (I A), via reaction with a compound that contains a -CN group

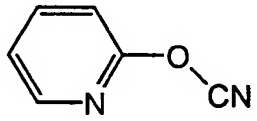
bound to a leaving group; in such compounds the -CN group behaves as an electrophilic group; preferred examples of such compounds are:

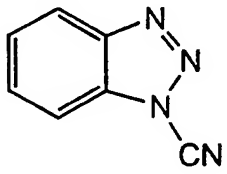
1) 

2) Cl—CN , or Br—CN

3) NC—CN

4) 

5) 

6) 

Among these, particularly preferred are the derivatives of formulas 2, 5, and 6.

The aforesaid compound that contains a –CN group bound to a leaving group is dissolved in an organic solvent, for example tetrahydrofuran, and added to a solution of the compound (I A); preferably, to the solution of the compound (I A) has previously been added a zinc salt, e.g., ZnBr or ZnCl. The compound that contains a –CN group bound to a leaving group is used in a molar ratio preferably of 2:1, approximately, with respect to the compound (I A).

Citalopram (IV) is obtained from the reaction mixture through appropriate extractions and washings.

Both modes of synthesis described above [(i)-(ii)-(iii)-(iv)] and [(i)-(ii')] are characterized by the common step (i), i.e., the formation of the intermediate key

product of formula (IA), which enables the citalopram to be obtained in high yields and without using drastic conditions of temperature. The aforesaid two modes of synthesis present the further advantage of not being racemizing. Consequently, if the starting product of (I) is used in an enantiomerically pure form (for example (S)), it is possible to obtain directly the corresponding enantiomer of the (S)-citalopram, without any need to separate the isomers, hence without any loss of product in the form of an undesired enantiomer and with a corresponding increase in yield.

The invention is now illustrated via the following experimental examples, which are provided purely as non-limiting examples.

EXPERIMENTAL PART

Preparation of 1-(4'-fluorophenyl)-1-1(3-dimethylaminopropyl)-5-phthalane aldehyde

Synthesis of the Grignard reagent of 1-(4'-fluorophenyl)-1-(3-dimethylaminopropyl)-5-bromophthalane

In an inert atmosphere and under vigorous stirring, to a suspension of 150 g (6.17 mol.) of magnesium chips in 1500 ml of tetrahydrofuran are added, at a temperature of 30-35°C, 15 ml (21.9 g; 0.20 mol.) of bromoethane. Upon activation of the magnesium, detected by spontaneous exothermia and foaming of the reaction mixture, at the temperature of 55°C an approximately 1 molar solution of 1125 g (2.98 mol.) of 1-(4'-fluorophenyl)-1-(3-dimethylaminopropyl)-5-bromophthalane in 3000 ml of tetrahydrofuran starts to percolate in a period of 7 hours. The reaction mixture is kept spontaneously refluxed throughout the addition. The mixture containing the Grignard reagent thus obtained is used in the subsequent phase of synthesis, after prior cooling at a temperature of approximately 20°C.

Formylation of the Grignard reagent of 1-(4'-fluorophenyl)-1-(3-dimethylaminopropyl)-5-bromophthalane

The solution of the Grignard reagent previously prepared in tetrahydrofuran is added drop by drop over a period of 3 hours to 455 ml (430 g; 5.96 mol.) of dimethylformamide. The temperature is kept between 20°C and the 25°C. After the addition is completed, the reaction mixture is left at room temperature under

stirring for approximately 3 hours. The mixture is then extinguished with 4500 ml of toluene and 4500 ml of water, and percolated in approximately 1 hour. To the reaction mixture is then again added, slowly and under continuous stirring, a volume of 240 ml of glacial acetic acid. The heterogeneous mixture is heated to a temperature of approximately 55-60°C to enable correct separation of the phases. The organic phase is separated from the underlying aqueous phase at 60°C, and further washed with 3 aliquots of 1500 ml each of water. The toluene solution having a volume of approximately 5 litres containing approximately 1200 g (crude) of 1-(4'-fluorophenyl)-1-1(3-dimethylaminopropyl)-5-phthalane aldehyde is used in the subsequent phase of the process. An aliquot is taken and titred via HPLC against an external standard for determination of the yield (molar yield: 83%).

2. Purification of 1-(4'-fluorophenyl)-1-1(3-dimethylaminopropyl)-5-phthalane aldehyde (via formation of bisulphite adduct).

To the previous toluene solution containing approximately 1200 g (crude) of 1-(4'-fluorophenyl)-1-1(3-dimethylaminopropyl)-5-phthalane aldehyde is added, under vigorous stirring, an aqueous solution of 793 g (4.17 mol.) of sodium metabisulphite in 1500 ml of water. The pH of the resulting aqueous phase is between 5 and 6 and is corrected between 4.5 and 5 by adding 450 ml of glacial acetic acid. The mixture is kept under vigorous stirring for approximately one hour and a half.

At the end of this phase, the pH is corrected to values between 6.5 and 7 with 290 ml of 30% aqueous sodium hydrate. The reaction mixture is left under vigorous stirring for approximately 15 minutes, at a temperature of 40°C. Then, stirring is stopped and the phases are left to settle. The toluene phase is separated from the aqueous phase, and discarded. The underlying aqueous phase is diluted with 4000 ml of water and further extracted with 5 aliquots of 1000 ml of toluene. At each extraction a check is made to see that the pH is between 6.5 and 7; otherwise, it is corrected with 30% aqueous sodium hydrate. Each individual washing and separation of the phases is carried out at 40°C.

The aqueous phase thus obtained at the end of this cycle of extractions is then corrected to a pH of not less than 9 with 700 ml of 10% aqueous sodium hydrate, maintaining the temperature between 20°C and 30°C. This is followed by the

addition of 2000 ml of toluene, and the mixture obtained is vigorously stirred for at least 30 minutes. After this period, a check is made to see that the pH of the aqueous phase is higher than 9; otherwise, it is further corrected with 10% aqueous sodium hydrate. The aqueous phase is separated from the organic one and re-extracted twice with aliquots of 1000 ml each of toluene. Each extraction and separation of the phases is performed at temperatures not lower than 40°C. The reunited organic phases have a volume of approximately 4000 ml.

An aliquot of 50 ml of the organic phase is concentrated at a reduced pressure, obtaining, after removal of the solvent, a dry residue corresponding to 23 wt%, consisting of a single pure product with an ionization profile at mass spectrometry and with an ^{1}H-NMR spectrum in accordance with the structure of 1-(4'-fluorophenyl)-1-1(3-dimethylaminopropyl)-5-phthalane aldehyde.

The organic solution at the end of this phase of the synthesis, containing 730 g of the pure product (molar yield 80% from bromophthalane) is used without further purification in the subsequent phase of the synthesis.

^{1}H-NMR in $CDCl_3$ δ 9.97 (1H; s; 5-CO<u>H</u>), from 7.80 to 6.94 (7H; m; aromatic protons); 5.20 (1H; d; J=12.2; 3-H_a), 5.10 (1H; d; J=12.2; 3-H_b); from 2.25 to 2.13 (2H; m; 3'-C<u>H_2</u>N); 2.11 (6H; s; NC<u>H_3</u>); from 1.50 to 1.31 (4H; m; 1'-e 2'-C<u>H_2</u>)

m/z ie 328 $(MH)^+$; 298 $(M\text{-}CHO)^+$; 241 $(M\text{-}CH_2CH_2CH_2(NCH_3)_2)^+$; 213 (m/z=298-$CH_2CH_2CH_2(NCH_3)_2)^+$; 193 $(m/z=213\text{-}HF)^+$.

3. Preparation of oxime of 1-(4'-fluorophenyl)-1-(dimethyl aminopropyl)-5-phthalane aldehyde

To the previous toluene solution containing 200 g (0.61 mol.) of pure 1-(4'-fluorophenyl)-1-1(3-dimethylaminopropyl)-5-formylphthalane, are added 60 g (0.37 mol.) of hydroxylamine sulphate. The mixture is reflux heated, and the pH is corrected to values between 4 and 5 with 70 ml of glacial acetic acid. After one hour of heating, the mixture is cooled. An aliquot of 10 ml of the aqueous phase is rendered basic to a pH higher than approximately 9 with 10% soda, and extracted with 10 ml of toluene. This small-volume, concentrated toluene phase is analyzed by mass spectrometry, providing a fragmentation by electron impact and ^{1}H-NMR spectrum, both in accordance with the structure of the oxime of 1-(4'-fluorophenyl)-1-(3-dimethylaminopropyl)-5-phthalane aldehyde. The product presents a purity of

76%.

The organic phase of the reaction mixture is separated from the aqueous phase, and eliminated. The aqueous phase containing 202 g of pure product (molar yield; 97%) is used without further purifications in the subsequent phase of the synthesis.

^{1}H-NMR in $CDCl_3$ δ 8.05 (1H; s; 5-C<u>H</u>NOH), from 7.51 to 6.94 (7H; m; aromatic protons), 5.16 (1H; d; J=12.0, 3-H_a), 5.13 (1H; d; J-12.0; 3-H_b), from 2.41 to 2.29 (2H; m; 3'-C<u>H_2</u>N); 2.23 (6H; s; NC<u>H_3</u>); from 1.55 to 1.30 (4H; m; 1'- and 2'-C<u>H_2</u>)

m/z ie 342 $(M)^+$; 324 $(M-H_2O)^+$; 256 $(M-CH_2CH_2CH_2(NCH_3)_2)^+$; 239 (m/z=256-OH)$^+$.

4. Synthesis of 1-(4'-fluorophenyl)-1-(3-dimethylaminopropyl)-5-phthalane carbonitrile

To the previous aqueous solution at pH 5 containing 200 g (0.59 mol.) of oxime of pure 1-(4'-fluorophenyl)-1-(3-dimethylaminopropyl)-5-phthalane aldehyde, are added 600 ml of toluene and 110 ml (120 g; 1.18 mol.) of acetic anhydride. The mixture is reflux heated, and a contained foaming is observed for not less than 3 hours. At the end of the reaction, the mixture is left to cool until a temperature of approximately 85°C is reached, and a cautious percolation of a volume of 200 ml of water is started. At the end of the addition, the reaction mixture is allowed to cool spontaneously, and then a solution of 460 ml of 30% sodium hydrate is added under vigorous stirring until a pH of 9-10 is reached. The organic phase is then washed with two aliquots of 200 ml each of water at a temperature of approximately 60°C. The organic phase is concentrated to a small volume at reduced pressure, to obtain an oil that slowly solidifies and weighs 253 g with an anhydro-potenziometric titre of 70%.

The oil obtained, weighing 250 g, is diluted with 750 ml of isopropanol and crystallized from this solvent to obtain the product, which has a melting point of 93°C.

^{1}H-NMR in CDCl3 δ 7.60 (1H; s; 4-H), from 7.52 to 6.98 (6H; m; aromatic protons); 5.25 (1H; d; J=12.9 3-H_a), 5.15 (1H; d; J=12.9; 3-H_b), 3.08 (2H; t; J=7.5; 3'-CH_2), 2.71 (6H; s; NC<u>H_3</u>, from 2.49 to 2.27 (2H; m; 1'-CH_2), from 1.82 to 1.71 (2H; m; 2'-CH_2)

m/z ie 324 $(M)^+$; 238 $(M-CH_2CH_2CH_2(NCH_3)_2)^+$; 218 $(m/z=238-HF)^+$.

5. Synthesis of {3-[1-(4-fluoro-phenyl)-1,3-dihydro-isobenzofuran-1-yl]-propyl}-dimethyl-amine 5-magnesium bromide (IA, X= Br)

The synthesis of the Grignard reagent is carried out as described in Example 1 starting from 72 g of {3-[5-bromo-1-(4-fluoro-phenyl)-1,3-dihydro-isobenzofuran-1-yl]-propyl}-dimethyl-amine (0.19 mol.).

The mixture containing the Grignard reagent thus obtained is used in the subsequent phase of synthesis, after prior cooling to 20°C.

6. Synthesis of 1-(3-dimethylamino-propyl)-1-(4-fluoro-phenyl)-1,3-dihydro-isobenzofuran-5-carbonitrile from tosyl cyanide

In an inert atmosphere and with perfectly dehydrated apparatus at room temperature, a solution of 2.76 g of *p*-toluenesulphonyl cyanide (30 mmol) is prepared in 50 ml of anhydrous tetrahydrofuran. The solution thus obtained is brought to the temperature of –20°C and at this temperature there is added, drop by drop and under vigorous stirring, 50 ml of a solution of {3-[1-(4-fluoro-phenyl)-1,3-dihydro-isobenzofuran-1-yl]-propyl}-dimethyl-amine 5-magnesium bromide (15 mmol) in tetrahydrofuran, obtained as described in Example 1, starting from 5.7 g of {3-[5-bromo-1-(4-fluoro-phenyl)-1,3-dihydro-isobenzofuran-1-yl]-propyl} - dimethyl-amine. Once the addition is completed, the solution obtained is kept at a temperature of –20°C for 30 minutes and then brought to 20°C. The reaction is then extinguished by percolation of the solution in a mixture of 50 g of 30% ammonia and ice, subsequently being brought to room temperature to enable decomposition of the non-reacted *p*-toluenesulphonyl cyanide. The mixture is then neutralized with diluted hydrochloric acid (1 molar) and extracted with 4 aliquots of 75 ml of toluene. The reunited organic extracts are washed with 2 aliquots of 100 ml of a saturated solution of sodium chloride, dehydrated with $MgSO_4$, and concentrated at reduced pressure, to obtain a dark-red oily residue.

The crude mixture obtained is then purified by flash chromatography on 50 g of silica gel 70-230 mesh (eluent: toluene-isopropanol-triethylamine, 95-5-2, v/v) to obtain 2.54 g of pure product (molar yield 52.3%) having an NMR profile in accordance with the desired structure.

7. Synthesis of 1-(3-dimethylamino-propyl)-1-(4-fluoro-phenyl)-1,3-dihydro-

isobenzofuran-5-carbonitrile from 1-cyanobenzotriazol

In an inert atmosphere and with perfectly dehydrated apparatus at room temperature, a solution of 1.72 g of 1-cyanobenzotriazol (12 mmol.) in 10 ml of anhydrous tetrahydrofuran is prepared. The solution thus obtained is brought to the temperature of 0°C, and at this temperature there is added, drop by drop and under vigorous stirring, 20 ml of a solution of {3-[1-(4-fluoro-phenyl)-1,3-dihydro-isobenzofuran-1-yl]-propyl}-dimethyl-amine 5-magnesium bromide (6 mmol) in tetrahydrofuran, prepared as in Example 1, starting from 2.3 g of {3-[5-bromo-1-(4-fluoro-phenyl)-1,3-dihydro-isobenzofuran-1-yl]-propyl}-dimethyl-amine. Once the addition is completed, the solution is slowly brought to room temperature and kept under stirring overnight.

The reaction is extinguished by percolation, under vigorous stirring, of a solution of ammonium chloride. The solvent is then eliminated in a rotary evaporator, and the residue obtained is diluted with 100 ml of toluene. The organic solution is washed with 4 aliquots of 75 ml of water. The organic extract is dehydrated with $MgSO_4$, and the solvent is eliminated by evaporation at reduced pressure, to obtain a dark-red oily residue. The crude residue obtained is purified via flash chromatography on 50 g of silica gel 70-230 mesh (eluent: toluene-isopropanol-triethylamine, 95-5-2, v/v), to obtain 1.39 g of pure product (molar yield 71.4%) having an NMR profile in accordance with the desired structure.

8. Synthesis of 1-(3-dimethylamino-propyl)-1-(4-fluoro-phenyl)-1,3-dihydro-isobenzofuran-5-carbonitrile from cyanogenous chloride

In an inert atmosphere and with perfectly dehydrated apparatus at room temperature, a solution of 12.3 g of cyanogenous chloride (200 mmol) in 200 ml of anhydrous tetrahydrofuran is prepared. The solution thus obtained is brought to a temperature of -10°C, and at this temperature there is added, drop by drop and under vigorous stirring, 330 ml of a solution of {3-[1-(4-fluoro-phenyl)-1,3-dihydro-isobenzofuran-1-yl]-propyl}-dimethyl-amine 5-magnesium bromide (100 mmol) in tetrahydrofuran, prepared as in Example 1, starting from 37.8 g of {3-[5-bromo-1-(4-fluoro-phenyl)-1,3-dihydro-isobenzofuran-1-yl]-propyl}-dimethylamine. Once the addition is completed, the solution is slowly brought back to room temperature and kept under stirring for one night. The reaction is then extinguished by percolation

of the solution in a mixture of 150 ml of 30% ammonia and ice (300 g) under stirring. The mixture is subsequently brought to room temperature and then to a pH of approximately 5 with diluted hydrochloric acid, and extracted with 4 aliquots of 200 ml of toluene. The reunited organic extracts are washed with 200 ml of a saturated solution of sodium chloride. The solvent is eliminated by evaporation at reduced pressure, to obtain 40 g of oily residue with an HPLC titre of 72% with respect to the standard. After crystallization, 20.5 g of product are obtained (molar yield 63.2%) with an HPLC titre of not less than 98% and with an NMR profile in accordance with the desired structure.

^{1}H NMR (200 MHz, $CDCl_3$): 7.60 (1H; s; 4-H), from 7.52 to 6.98 (6H; m; aromatic protons), 5.25 (1H; d; J=12.2; 3-C$\underline{H}_a$), 5.15 (1H; d; J=12.2; 3-C$\underline{H}_b$), 3.08 (2H; t; J=7.5; 3'-CH_2), 2.71 (6H; s; -NCH_3), from 2.49 to 2.27 (2H; m; 1'-C$\underline{H}_2$N) from 1.82 to 1.71 (2H; m; 2'-C$\underline{H}_2$).

M/z ie 324 $(M)^+$; 238 $(M\text{-}CH_2CH_2CH_2(NCH_3)_2)^+$; 218 $(m/z=238\text{-}HF)^+$.

9. Preparation of 1-(4'-fuorophenyl)-1-1(3-dimethylaminopropyl)-5-phthalane aldehyde by reaction with butyl lithium (Reference example)

To a solution of 40.5 g (0.107 mol.) of 1-(4'-fluorophenyl)-1-(3-dimethylaminopropyl)-5-bromophthalane in 135 ml of THF a solution of 40 ml (0.108 mol.) in heptane of butyl lithium 2.7 molar is percolated under vigorous stirring at a temperature of between -3°C and +3°C. At the end of the addition, the reaction mixture is left under stirring at a temperature of 0-5°C for approximately one hour before percolating 8.5 ml (0.111 mol.) of dimethylformamide.

The addition of the dimethylformamide is markedly exothermic; the temperature must be kept between 0° and 5°C throughout the addition. The reaction mixture is then stirred at a temperature of 5°C for approximately 30 minutes, and then the temperature is allowed to rise spontaneously. At execution of the first check of the process by gas-chromatography after 30 minutes, the crude mixture presents approximately 4% of phthalane aldehyde (II) and 2% of bromophthalane (I), whilst the remainder consists mainly of 1-(4'-fluorophenyl)-1-(3-dimethylaminopropyl)-phthalane.

This example shows that not all metallo-organic reagents are suitable for effectively obtaining 1-(4'-fuorophenyl)-1-1(3-dimethylaminopropyl)-5-phthalane

aldehyde. The choice of using activated magnesium in Step (i), and preferably in the conditions of reaction indicated, are consequently of determining importance for purposes of the efficiency of the present process.

CLAIMS

1. A process of synthesis of 1-[3-(dimethylamino)propyl]-1-(4-fluorophenyl)-1,3-dihydro-5-isobenzo-furancarbonitrile (citalopram), characterized by the following steps:

(i) reaction of 1-(4'-fluorophenyl)-1-(3-dimethylaminopropyl)-5-halophthalane (I) with activated magnesium, to form the Grignard reagent of formula (I A), where X is a halogen atom, preferably bromine;

(ii) reaction of the compound (I A) with a substituted formamide, to form the 1-(4'-fluorophenyl)1-3-(dimethylaminopropyl)-5-phthalane-aldehyde (II);

(iii) reaction of the compound (II) with a reagent of structure NH_2-Y, where Y is chosen from among -OH, -OCH_3, -$N(CH_3)_2$, -OSO_3H, with formation of a compound of formula (III), where Y has the aforesaid meanings; and conversion of

(iv) the compound (III) into citalopram (IV).

2. A process according to Claim 1 in which, in step (i), the compound (I) is dissolved in an organic solvent ("solution *b*") and added to a mixture of activated magnesium in organic solvent ("solution *a*")

3. A process according to Claim 2, where the compound (I) is used in a weight ratio with respect to magnesium of between 5:1 and 15:1, preferably 7.5:1.

4. A process according to Claim 2, where the concentration of compound (I) in the solution *b* is between 0.7M and 1.2M.

5. A process according to Claim 2, where the volume of solution *a* is between 40% and 60% with respect to the volume of solution *b*.

6. A process according to Claim 2, where the time within which solution *b* is added is longer than 5 hours.

7. A process according to Claim 2, where: the compound (I) is used in a molar ratio with respect to magnesium of 1:2; the concentration of the compound (I) in solution *b* is 1M; the volume of solution *a* is 50% with respect to the volume of solution *b*; the time within which solution *b* is added is between 6 and 8 hours.

8. A process according to each of Claims 1-7, where said substituted formamide is chosen from among dimethylformamide, *N*-formyl-*N*-methyl-2-aminopiridine, trimethylformyl-ethylenediamine, *N*-formylpiperidina, *N*-formylmorpholine.

9. A process according to each of Claims 1-8, where said substituted formamide is

used in molar ratio of approximately 2:1 with respect to the compound (I).

10. A process according to each of Claims 1-9, carried out continuously in the same reactor, without isolation and/or purification of intermediate products.

11. A process according to each of Claims 1-10, where in step (iii) the molar ratios between the compound (II) and the compound NH_2-Y are between 1:1 and 3:1

12. A process according to each of Claims 1-11, where the compound (III) is an oxime and step (iv) is carried out by dehydration with concentrated acetic acid or with acetic anhydride.

13. A process according to each of Claims 1-11, where the compound (III) is a hydrazone and step (iv) is carried out by oxidation with methylrhenium trioxide and hydrogen peroxide.

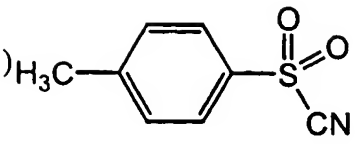
14. An intermediate product of synthesis of citalopram of formula (I A), where X is a halogen atom, preferably bromine.

15. A process of synthesis of 1-[3-(dimethylamino)propyl]-1-(4-fluorophenyl)-1,3-dihydro-5-isobenzo-furancarbonitrile (citalopram), characterized by the following steps:

(i) reaction of 1-(4'-fluorophenyl)-1-(3-dimethylaminopropyl)-5-halophthalane (I) with activated magnesium, to form the Grignard reagent of formula (I A); and

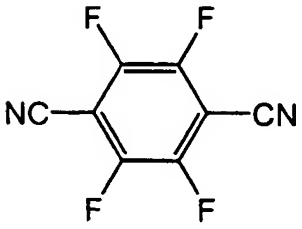
(ii') reaction of the compound (I A) with a compound containing a -CN group bound to a leaving group, to form citalopram (IV).

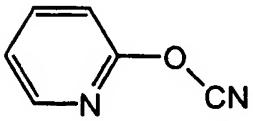
16. A process according to Claim 15, where said compound containing a -CN group bound to a leaving group is chosen from among the compounds having formulas 1)- 6).

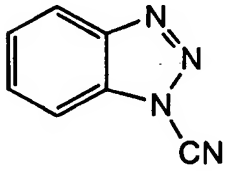
1) 

2) Cl—CN , or Br—CN

3) NC—CN

4) 

5) 

6) 

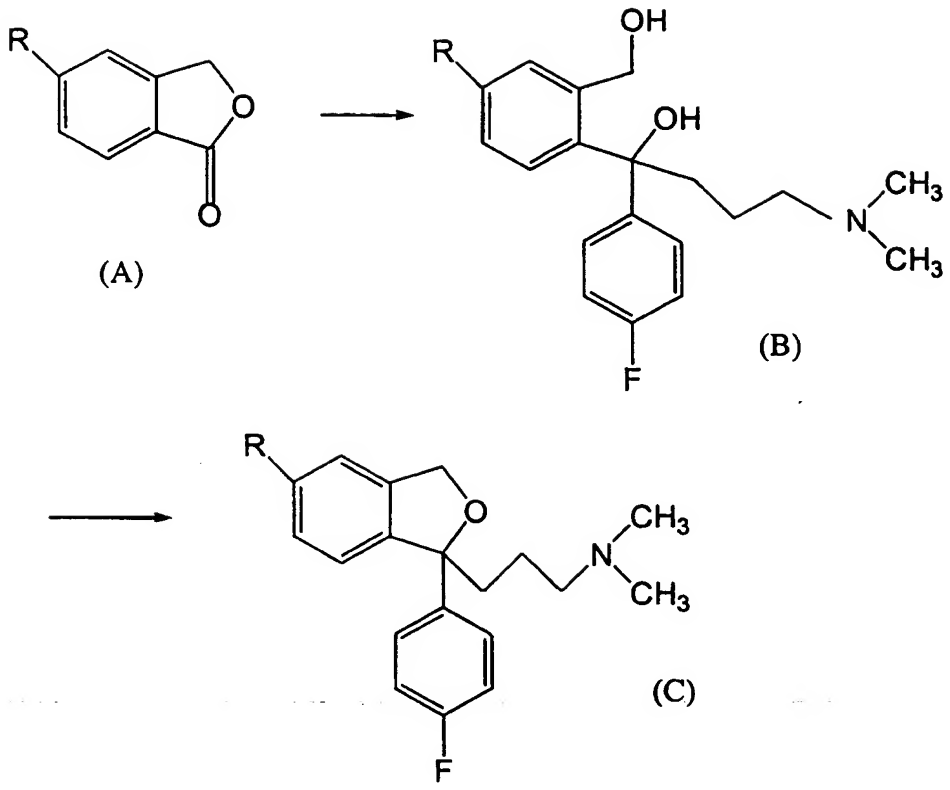


FIG. 1

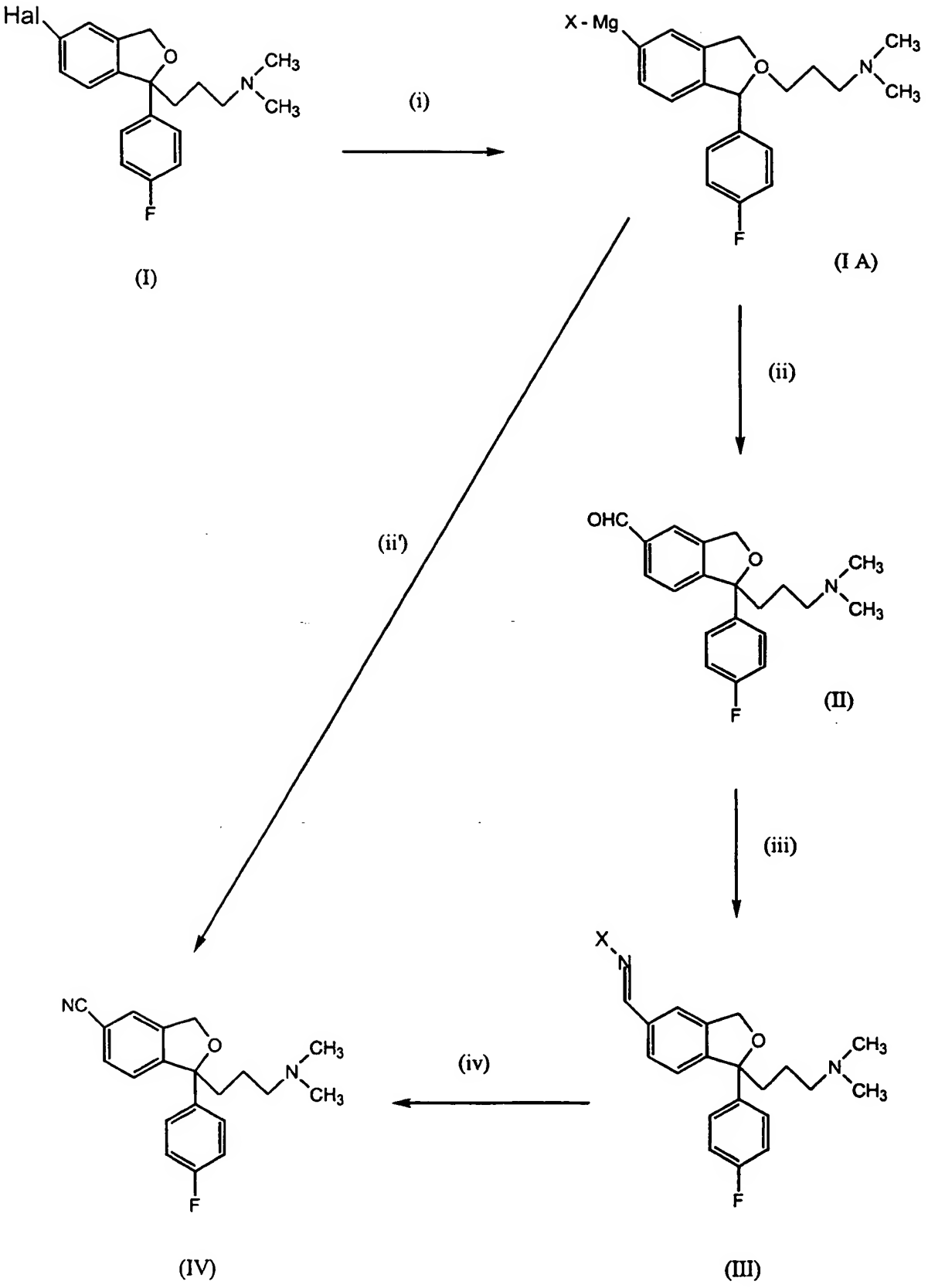


FIG. 2